The following Questions and Answers were addressed in a telephonic Question and Answer Session on Friday, June 12, 2009.

All page numbers refer to the RFA 09-01 as it is printed in the pdf format which is downloaded from CIRMs website.

Application Forms and Instructions

1. **Are appendices allowed; and if so, what are the limits on types of information to be included?**

   - *Appendices are not allowed and will not be provided to reviewers*

2. **This question refers to Part D of the application: Should we provide institutional letters from all institutions or only PI/ Co-PI/partner institutions?**

   You should provide Institutional Letters of Commitment per the instructions in RFA 09-01 (Section VIII.C.13, page 19) for each of the research team leaders designated in your application: CIRM PI, CIRM Co-PI(s), and Partner PI, observing the two page limit per leader. Other letters of commitment or agreement may be included.

   Process comment: Compile all letters for the research team into a single document. Additional letters should be placed after the Institutional Letters of Commitment in the single document. We recommend that you convert the final document into a PDF file to ensure that formatting is preserved.

3. **This question refers to Part D: Institutional Letter(s) of Commitment. Do you have any template for this document? Do you need the original document signed, or is a scanned copy of the original page enough for you?**

   - *There is no template for the Institutional letter of commitment. A scanned copy of the signed original should be assembled as per the instructions in the RFA.*

4. **Only a Partner PI was identified in the pre-application, yet the partner PI has established a consortium at multiple sites. Should we obtain letters from all sites?**

   - *Answer is the same as for question 2. Additional letters are not required by CIRM, but may be included. You should also ask this question of the Funding Partner with whom you are working, as they may have additional requirements.*

5. **This next question refers to Part E of the application, the Related Business Entities form. If we originally checked "The PreApp does not propose funding for any for-profit organization", is it too late to change to "The Application proposes funding for one or more for-profit organizations." in the final proposal?**

   - *Part E, the Related Business Entities Form, should be updated and re-submitted as part of the full application. It is not too late to change the answer to the question, and should accurately reflect the status of for-profit organizations in your proposal.*

6. **This question refers to Part A: Subpart II. Shall we include all the key personnel, key personnel trainee and budget justification of all the Collaborative Funding Partner personnel or only the data of the Partner PI?**

    - *Key Personnel listed in Subpart II should include all key personnel who will receive funding from the Funding Partner with whom you are working. Instruction in the form read: "Identify each key person who will participate in the proposed project. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any technical staff, co investigators, or consultants who meet this definition."*

7. **Do you need the original document signed (Subpart II), or is a scanned copy of the original page enough for you?**

    - *A scanned copy of the signed signature page provided to the PI for submission is fine. This also applies to Subpart I from CIRM-funded Co-PIs. The only original signatures required in hardcopy at the time of submission are those from the PI and the Applicant Institution AOO on the Part A: Project Information Form.*

<u>Principal Investigator</u>

8. **PI effort: Is 30% effort required for team oversight, or can it be distributed between administrative activities and research?**

    - *The PI is expected to act as the Team Leader for the project. The RFA states (on page 2) "The team leader provides vision, strategy, and overall project direction, has scientific and financial accountability, and should be a practicing professional with a record of effective scientific leadership." The answer to this question is yes, the PI's efforts may be distributed between scientific research and management activities.*

9. **Does CIRM see any issues with a PI and one of the Co-PIs listed performing the work from the same institution, or is it expected/favored that Co-PIs be from other institutions?**

    - *CIRM does not have a problem with a PI and Co-PI from the same institution performing work on the project.*

    - *It is neither expected nor favored that a PI and the Co-PI be from different institutions. Reviewers are directed to focus on whether the relevant expertise to conduct the research is represented on the team.*

<u>Miscellaneous Personnel Questions</u>

10. **If 10 key personnel from multiple sites were included in the pre-application are we allowed to add personnel to that list? Will this be considered a negative?**

    - *You may add additional key personnel to the lists. There is no maximum. Reviewers are asked to evaluate whether the relevant expertise is staffed to the project, at a sufficient but not excessive amount to accomplish the proposed activities.*

11. The CIRM-funded budget is broken down by PI, co-PI sections. If a post-doc will be shared with a PI and Co-PI (or other research leader), how is that recorded?

- *To answer this question, CIRM interpreted a "shared post-doc" to mean a resource that is conducting separate activities under the guidance of two supervising scientists on the team leadership (2 co-PIs or a PI and Co-PI). A "shared post-doc" would appear 50% under 1 Co-PI and 50% under Co-PI 2 (if shared equally). Relative efforts should be ascribed to each of the Co-PIs (or PI and Co-PI) in the Key Personnel sections.*

Co-Principal Investigators (Co-PIs)

12. Can two Co-PIs share the Co-PI position with another investigator whose work will be more critical during the early phases of a project?

- *As a starting point, the RFA is clear that only 2 Co-PIs are allowed to be named per application. This means only 2 individuals may be named, not a combination of more than 2 individuals at different time points during the project.*

- *The RFA also states that the minimum commitment for a Co-PI is 20% effort, which is meant to apply to any given budget period. If a Co-PI's role is only relevant in Years 1 and 2 of the project, we would expect a 20% commitment in Years 1 and 2.*

- *For Co-PI effort, there are only 2 choices: 20% or greater; or zero % commitment. If zero % commitment for a budget period, we would expect zero other expenses for that Co-PI's budget. Otherwise, the PI would need to handle that remaining budget for activities if at the same institution, or as a subcontract if at different institutions.*

13. Can a Co-PI's commitment ever be less than 20%?

- *CIRM did anticipate that there would be circumstances in which a minimum 20% effort (for the Co-PI) might not fit every project. On page 6 of the RFA there is an option to seek approval to apply with a commitment of less than 20%. In order to pursue that option, you need to submit the justification prior to June 22 per the instructions in the RFA.*

- *"In extraordinary circumstances, and at the discretion of the President of CIRM, a senior research scientist may be permitted to apply as a PI with a commitment of less than 30% effort (or as a Co-PI with a commitment of less than 20% effort), if s/he convincingly demonstrates that doing so is optimal for the research project. Such exceptions **must** be requested prior to June 22, 2009 (see contact information below) to allow the President of CIRM adequate time to review and to consider the request prior to July 16, 2009, the deadline for submission of a full application."*

14. We understand that Co-PIs should show a minimum of 20% effort. Is it expected that the Co-PI have a full-time appointment at the institution where they are listed, or is it acceptable that they have a minimum 20% appointment at the institution indicated?

It depends on whether the CO-PI is at a non-profit or a for-profit institution.

- *A Co-PI at a for-profit institution must be an employee (at least 50% time) of the sponsoring institution.*

- *A Co-PI from a non-profit institution must be an independent investigator (by the time of the pre-application deadline), have documented authority from the sponsoring institution to staff the proposed project, and have documented commitment from the sponsoring institution to provide laboratory space and shared resources sufficient to carry out the proposed research. (Fulfillment of these terms should be documented in the Institutional Letter of Support).*

15. If there is a change since the submission of the preliminary application in terms of the institution where the Co-PI is listed (Co-PIs are the same but institutions may have changed), does this require any special approval process or may this move forward with the change/corrections in the full application?

- *You should submit notification to CIRM. CIRM will instruct you to apply listing the new institutional affiliation for the Co-PI. You should include in your discussion the points in the "Collaborations, Resources and Environment" section of the Research Proposal (Part B) (see page 18 of the RFA) as they relate to the new Co-PI institution. You will also need a Letter of Institutional Commitment from that new institution, as specified in the RFA on page 19.*

Project Manager

16. Project manager: Is the role of the project manager to coordinate administrative oversight for the project, or are they also supposed to play a scientific role? Do you see this as a full time position?

- *The RFA states (on page 2) "The Project Manager will oversee project operations and ensure that the team activities progress smoothly." The Project Manager's primary responsibility is to work with the PI to facilitate operational oversight of the project. Successful project managers have skills to assist with managing schedule, budget, and timeline; and to assist the PI with communication amongst team members and with relevant stakeholders.*

- *Whether they play a scientific role is unique to each individual or team. It is not a requirement of the RFA.*

- *CIRM did not specify a % effort for this role. Each team should decide an appropriate % effort for this individual, based on the nature and complexity of the project.*

- *We can offer examples from industry, in which Project Managers are commonly used. Project Managers often manage 2 or 3 projects at a time, unless it is a complex multi-site (possibly multinational) effort.*

Scope of Projects

17. The goal of the Disease Team Award is to file an IND within 4 years. Is any type of IND sufficient to fulfill this requirement?

- *The intent of the program is to support projects that result in INDs that enable Phase I clinical testing. Either investigator-initiated or "commercial" INDs are acceptable. Emergency INDs or Treatment INDs would NOT be acceptable.*

18. Is it correct that repurposing an agent that has been developed for an unrelated indication would be acceptable, as long as it leads to an IND?

- *The therapeutic candidate (the term we use for "agent" in this question) and the indication (disease to be treated) must be those which were proposed in the preliminary application. The proposed therapeutic candidate will be judged by the review panel according to the Scientific Rationale and Significance criteria presented on page 10 of the RFA, which include: the scientific rationale, the use of human stem cells, unmet medical need, clinical competitiveness, and the impact for patients.*

19. This question refers to the scope of responsive projects, as it relates to the development pathway (the first full paragraph on page 2 of the RFA), which starts: "This program is specifically directed at projects that include therapeutic candidates with demonstrated activity against a disease target. Projects of suitable scientific maturity for this award will have demonstrated, at a minimum, reproducible evidence of disease-modifying activity;…" and concludes: "The program…excludes projects already in clinical trials." We interpret this to mean that grant money cannot be used to support clinical trials.

- *Activities that are included in the scope of the RFA are detailed in diagrams in Appendix A, pages 22-24 of the RFA. A minimum "starting point" is articulated above, as "reproducible evidence of disease-modifying activity."*

- *The end goal of the projects are to file an IND that enables Phase I clinical testing. CIRM is aware that projects that file successful INDs will move into Phase I testing. CIRM will work very hard over the next 18 months to develop a program to fund clinical studies, but funds from this RFA cannot be used to conduct clinical studies.*

20. Would it be acceptable to include a cGMP batch production of the candidate therapeutic (the intended therapeutic product for a Phase I trial) under this RFA?

- *The answer to this question is a "qualified yes". The first point is appropriate timing. We would not expect teams to produce this prior to a "go" decision for IND-enabling studies. It would be a reasonable activity to occur at the same time as other requirements of the IND submission, so that timely start of clinical studies could be expected for successful projects.*

21. How close does the full app have to be to the pre-application? Can we present the same project in a different way in the research plan? Is the focus of keeping it the same on the leadership, drugs that are being tested and disease? How much flexibility do we have with plan presentation/design?

- *The project proposed in the full application must be the same as that described in the pre-application with respect to:*
  1) team leadership (PI and if applicable Co-PI(s), and Partner PI)
  2) proposed therapeutic candidate(s) and indication(s)
  3) overall preclinical R&D plan

This is based on statements in the RFA (page 8; section VI, paragraph 2) and the instructions to the full application. The intent is for CIRM to get applications for the proposals that were determined, in pre-application review, to show the most promise within the scope of the RFA. If the applicant no longer seeks to pursue a project that shares these components of the pre-application, the applicant should consider withdrawing from this round and applying in a later RFA.

- *CIRM expects, of course, that the full application will include a more detailed research plan, so that the reviewers can evaluate the Feasibility of the plan according to the review criteria listed on page 11 of the RFA.*

22. This question is related to the Preclinical Research and Development Plan section in Part B. Please describe in detail the format and content desired in the Milestones section. For milestones, how broad or specific do you prefer them to be? Could you provide 2-3 examples?

Milestones are quantifiable measures and reliable indicators of the project's successful progress to the stated goal of IND filing for a competitive stem cell-based therapeutic by a stated date. The format in which milestones are presented in the application is the choice of the applicant.

Milestones are often "critical path activities". Critical path activities are defined as activities that, if not completed by a specified time with the desired outcome(s), the project will: 1) not meet the timeline and/or 2) will not be feasible. Given the many parallel areas of research necessary for IND filing, CIRM would expect to see several milestones in any given budget year. For applications that are funded, CIRM will work with grantees to modify milestones as necessary, to ensure that they effectively define a progression toward the stated goal of IND filing.

For example, in a proposed project with the overall goal to file an IND within 3 years of start of funding, examples of milestones could be:

- *By 1.0 year after start of funding, have completed preclinical studies in three relevant models that reproducibly and with statistical significance indicate that the candidate therapeutic has a competitive advantage over other therapies currently marketed or in development. If not, no go.*

- *By 1.0 year after start of funding, have completed process scale-up of candidate therapeutic to reproducibly yield a minimum of Y cells per batch and meet minimum defined criteria for purity and potency.*

- *By 1.5 year after start of funding, have produced X amount of drug candidate under GLP (or GMP), to enable toxicology study, ongoing pharmacology and mechanistic studies. If not, discussion with CIRM*

- *By 2.5 year from start of funding, complete IND enabling toxicology studies and have preliminary report that indicates no unmanageable toxicity. If not, no go for targeted indication*

CIRM has identified key points at which it would like to participate in project decision making through an evaluation meeting that CIRM would convene:

1) at the start of IND-enabling studies, when funding needs typically increase; and

2) after IND-enabling toxicology studies prior to IND filing. The second time point is typically a decision point for whether the program can proceed to IND filing and clinical studies.

Out of State Expenditures and California-based consulting/subcontract questions

23. Are we allowed to spend CIRM-awarded funds outside of California for a contractor providing a service?

- *The CIRM Grants Administration Policy states that subcontracts or consulting agreements with individuals or organizations located outside the State of California must be justified and are limited to $15,000/year for any one contract, and $25,000/year in aggregate. The amount of any subcontract (within California or out of state) must be justified in the Budget Justification section of the appropriate Part A Subpart form at the time of application.*

- *For amounts above those limits, applicants must seek and obtain Prior Approval during the administrative review that occurs before an approved grant is funded. At that time, you would need to justify the need for an out-of-state subcontract. There is no guarantee that approval would be granted, particularly if the project could be completed with in-state resources.*

- *We received this question in many flavors. CIRM emphasizes that presence (or absence) of an out-of-state contract is not part of the review criteria on which your application will be judged. Reviewers are asked to evaluate whether the appropriate expertise and resources to complete the research objectives are included in the project.*

24. Can an out-of-State purchased service for production and certification of a clinical grade reagent be included in the application?

- *See above.*

25. Are there any budgetary limits to California-based consultants?

- *There is no specific budgetary "cap" for subcontracts or consultants in California. Budgets for consultants should be justified in the Budget Justification section, with an explanation of the services/expertise to be provided, the rate, and the level of effort for each consultant/ subcontractor. (This language is repeated in the instructions for the Budget Justification sections).*

26. How much will having corporate partners be weighted in the awarding of CIRM 09-01? How much weight to California corporate partners?

- *The project will be judged on the scientific merit according to the review criteria presented in the RFA on pages 10-12. The presence of corporate partners, or California corporate partners is not a review criterion for this proposal. Reviewers will evaluate whether the relevant expertise and resources are available to accomplish the project objectives.*

Budget questions

27. Budget: $20 million total costs/4 years. Should the money be budgeted equally for each of the years in the project period, or can the budget vary (increase in later years due to development costs, for example)?

- *RFA states on page 3: "Projects will be funded for up to four years, with justifiable total funds requested (includes direct project costs, direct facilities costs, and indirect costs) of $3 million to a maximum of $20 million per project." This RFA did not specify an annual maximum since the funds requested in any given budget year are expected to vary, depending on which phase of development your project is in.*

- *The budget should reflect the necessary activities in any given budget year and need not be equally distributed across the project period. The intent of this RFA is not simply to allocate the maximum of $20 million over 4 years; instead, the budget should reflect appropriate expenditures to cover activities that are critical in any given budget period. The project costs are not assumed to be the maximum of $20 million. The project time period should realistically reflect the time to complete the activities, and is not assumed to be the maximum of 4 years for every project.*

- *Expenditures should be justified in the Budget Justification section. Finally, reviewers will evaluate the budget according to the review criteria on page 11: "Budget: team leaders have developed a budget that is focused and appropriate for activities to achieve IND filing."*

28. Core services budget: We assume that the costs of core personnel will be listed under the personnel budgets (Subpart I), and the supply costs will be listed on the supply budget (Part A- detailed Budget Worksheet). Is this correct?

- *The answer is "no". Core services expenses may include the personnel component to perform those services. Key personnel should be limited to individuals who are making a significant and measurable contribution to the specific project and optionally who would be getting a salary (not a fee) for participating in the project. Since the core service is something that is being used by the grantee and not something CIRM is supporting directly, then you should not report itemized personnel costs associated with the service.*

29. There are recharges (such as computer networking/phone) that don't seem to fit well on the budget pages. Where should these be listed?

- *These are categorized as indirect costs and do not have line items in the budget forms.*

30. About Part A: Detailed Budget Worksheet. Do we have to include the budget of all the partners in Partner PI sheet, or just the expenses of the Partner PI*?*

- *You should provide a consolidated budget (total funds requested) for the entire project to be funded by the Funding Partner. You should also ask this question of the Funding Partner with whom you are working, as they may have additional, more detailed requirements.*

31. Should we budget for travel to CIRM for reporting?

- *CIRM is not requiring in-person meetings except for evaluation meeting(s). It would be appropriate to budget for the research leadership (PI, Project Manager, and if applicable, Co-PI(s) and Partner PI) to attend an in-person session for evaluation meeting(s).*

Intellectual Property (IP) Questions

32. We are planning to use a for-profit partner as a subcontract for some of our studies and scale-up activities in our proposal, and have several questions that you might cover in the teleconference call Friday. First, are there budgetary limitations on subcontracts for the disease team proposals?

- *There is no specific budgetary "cap" for subcontracts to for-profit (or non-profit) organizations. Out of state limits on subcontracts apply as discussed previously. All provisions of allowable expenses in CIRM's Grants Administration Policy (GAP) apply to subcontracts.*

33. Are there intellectual property policies of CIRM that might impact subcontracts?

Yes, but it depends on the work subcontractor does.

- *CIRM has adopted policies governing intellectual property of its grantees and collaborators, which policies have been codified in regulation. Make sure your counsel's office is aware of our IP regulations found on the CIRM website: Regulations Governing CIRM Grants | CIRM. Chapters 3 (sections 100300 et seq.) and 4 (sections 100400 et seq.) of the regulations govern non-profit and for-profit grantees, respectively.*

- *CIRM is in the process of consolidating the two sets of regulations into one comprehensive scheme that will apply to both non- and for-profit grantees. The consolidated regulations will govern the Disease Team RFA, and may be found further down the Regulations page of the website (beginning with section 100600) (http://www.cirm.ca.gov/reg/pdf/consolidated_regulations_OAL_notice.pdf). A summary document, titled the Initial Statement of Reasons (http://www.cirm.ca.gov/reg/pdf/Initial_Statement_Reasons_consolidatedip.pdf), may be found on the same web page for the consolidated regulations and gives an overview of what the policy addresses and how the regulations operate.*

- *For additional questions, use the contact information listed in the RFA, website, and email, and we will forward to the appropriate individual.*

34. Do we need to specifically address IP issues in our application?

- *On page 18 of the RFA, the place to address IP is in Part B: the Research Proposal, in the "Collaborations, Resources and Environment section". Among other aspects of this element, in 2 pages applicants are asked to: "Discuss relevant intellectual property and licenses that are available to the project"*

35. Will the handling of IP be included as part of the grant review?

- *One of the four review criteria is "Collaborations, Resources and Environment" listed on page 12 of your RFA. Reviewers are instructed to assess whether "relevant assets are available to the project".*

36. Is agreement for IP management required among collaborating institutions at the time of application?

- *No. Please see proposed regulation 100602, subdivision (a), which states that agreements must be in place "prior to an NGA" between a Grantee and Grantee Personnel and Collaborators requiring prompt disclosure to the Grantee of any CIRM-Funded Invention or CIRM-Funded Technology (see page 8 of: http://www.cirm.ca.gov/reg/pdf/consolidated_regulations_OAL_notice.pdf). Thus, the agreement does not need to be in place at the time of application, but must be in place before the Notice of Grant Award is signed.*

Review

37. Was there a scientific review of the pre-app, or was it administrative (confirming that proposal was within the scope of the RFA, etc)?

- *There was a scientific review that included, for each PreApp, an evaluation by 3 external expert reviewers and 3 CIRM Science Officers. PreApps were assessed against the criteria described in the RFA.*

38. When will the review be conducted, and when will we be told about our score? Will we get written feedback regarding our proposal with the score?

- *The review will be conducted September 9-11, 2009.*

- *Information will be provided to applicants in the second half of October 2009. Applicants receive their average score, recommendation to the ICOC, and a summary of review that combines comments from reviewer critiques as well as the discussion of the application during the meeting.*